

REMARKS

Applicants respectfully request entry of the amendments and remarks presented herein. Claims 37, 43-49, and 51-55 remain pending, and claims 56-73 stand withdrawn. Claims 52-54 are amended herein to remove language related to functional derivatives or fragments and to include proper Markush group language. No new matter has been added.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 37, 43-49, and 51-55.

Withdrawn rejections

Applicants acknowledge the Examiner's withdrawal of the previous rejections for alleged obviousness-type double patenting and anticipation, as set forth in the Advisory Action mailed December 31, 2007.

Rejections under 35 U.S.C. § 112

In the Advisory Action, the Examiner maintained the rejection of claims 37, 43-49, and 51-55 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. In particular, the Examiner alleged that the disclosure does not direct one of skill in the art to functional derivatives or fragments of the proteins as currently claimed.

Applicants respectfully disagree. For at least the reasons stated in Applicants' response filed on November 26, 2007, the previous claims were adequately described. Nevertheless, to further prosecution, Applicants have amended claims 52-54 to remove the language related to functional derivatives or fragments. In light of these amendments, Applicants respectfully request withdrawal of this rejection of claims 37, 43-49, and 51-55 under 35 U.S.C. § 112, first paragraph.

The Examiner also maintained the rejection of claims 37, 43-49, and 51-55 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Specifically, the Examiner asserted in the Advisory Action that undue experimentation would be required to make and use the hydroxyethylstarch- (HES-) protein conjugates as claimed, as "the prior art has shown a large

quantity of experimentation is often necessary to overcome the unpredictable nature of protein conjugation with hydroxyethyl starch polysaccharides.”

Applicants disagree, and respectfully direct the Examiner to *In re Wands* (858 F.2d 731 (C.A.Fed. 1988)), in which the court stated that “The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed” (citing *In re Jackson*, 217 USPQ at 807 ((Bd. App. 1982))). As stated in Applicants’ responses filed on July 6, 2007 and November 26, 2007, the specification describes how to make the presently recited HES-protein conjugates, provides numerous working examples of HES-protein coupling reactions proceeding through the formation of a Schiff’s base, and teaches methods for evaluating the efficiency of the coupling reaction and assessing the function of the modified protein. Thus, Applicants’ specification provides a reasonable amount of guidance for making the presently recited conjugates. As such, Applicants again submit that no undue experimentation would have been required for a person of skill in the art at the time Applicants filed to make and use the presently recited HES-protein conjugates.

Moreover, Applicants note that the Examiner has presented mainly conclusory statements in the non-final and final rejections for alleged lack of enablement. The only evidence asserted by the Examiner in the rejections is the Maout et al. reference (“Hydroxyethylstarch Conjugated to Human Hemoglobin for use in Blood Transfusion: Comparison with Dextran Conjugates,” Carbohydrates and Carbohydrate Polymers – Analysis, Biotechnology, Modification, Antiviral and Other Applications, 1993, Chapter 12, pp. 132-140), which was cited in the Office Action mailed on March 6, 2007. The Examiner asserted that the Maout et al. reference discusses the unpredictability in outcome of protein function after conjugation with a HES polysaccharide. As described by Maout et al., HES was conjugated to hemoglobin using a carboxylate functional group derived by reacting HES with benzene 1,2,4,5-tetracarboxylic anhydride (BTCA), but the HES-BTC-hemoglobin conjugate was not effective as a blood substitute. The Examiner alleged that, given this result, it is not predictable that any functional group can be used to conjugate any hydroxyalkylstarch with any protein.

It is a leap, however, to go from the results presented in the Maout et al. reference, to the Examiner's conclusion. The negative results in the case of HES-BTC-hemoglobin are attributed by Maout et al. to HES crosslinks introduced in the activation step with the BTC linker. *See*, e.g., the last sentence of the Abstract at page 132, and the second paragraph at page 137. In contrast to the coupling described in the Maout et al. reference, the presently recited conjugates are formed via direct coupling of the aldehyde group at the reducing terminal end of HES and an amino group of the protein, and crosslinking of the HES does not occur. That is, the mechanism of the instant coupling is fundamentally different from the coupling disclosed by the Maout et al. reference. As such, this reference provides no reason that would lead one of skill in the art to believe that the presently recited conjugates would not be functional.

Given the above, the present claims are fully enabled. Thus, Applicants respectfully request withdrawal of this rejection of claims 37, 43-49, and 51-55 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants submit that claims 37, 43-49, and 51-55 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please apply \$810 for the Request for Continued Examination fee, \$1050 for the Petition for Extension of Time fee, and any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

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